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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/506,942 02/18/00 BALLOUL

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EXAMINER

FOLEY,S

ART UNIT

PAPER NUMBER

1648

DATE MAILED:

10/12/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/506,942	BALLOUL ET AL.	
	Examiner	Art Unit	
	Shanon A. Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- 1) Responsive to communication(s) filed on _____.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 10-20 and 25-31 is/are pending in the application.
 - 4a) Of the above claim(s) 1-9, 21 and 22 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 10-20 and 25-31 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
 - a) All b) Some * c) None of the CERTIFIED copies of the priority documents have been:
 1. received.
 2. received in Application No. (Series Code / Serial Number) _____.
 3. received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

- | | |
|--|--|
| 15) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 18) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 16) <input checked="" type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 19) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 17) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 20) <input type="checkbox"/> Other: _____ |

DETAILED ACTION***Double Patenting***

Claims 10-20 and 25-31 of this application conflict with claims 10-20 and 25-31 of Application No. 09/043,933. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10, 11, and 23-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9, 23, and 24 of copending Application No. 09/043,933. Although the conflicting claims are not identical, they are not patentably distinct from each other because the vaccinia vector(s) in the present application has identical polypeptides to the parent application. Each application states that the

identical proteins are expressed from independent expression control elements, which could be accomplished by any vector, such as vaccinia.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-20 and 25-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10, 25, 26, and 30 refer to polypeptides from the early (E6 and/or E7) "region" and the late (L1 and/or L2) "region" of a human papilloma virus. What are these regions? A fragment consisting of 3 amino acids would satisfy the claim requirement of a polypeptide obtained from the early and late "regions". The claims have been interpreted in light of the specification and since the specification does not set forth clear metes and bounds of the intended early and late "regions" of the papilloma virus, the claims are considered to be indefinite.

Claims 10 and 15-19 are drawn to DNA "fragments" coding for regions of the papillomavirus. What are these "fragments"? A fragment could consist of 3 sequential amino acids from the wild-type protein. There is insufficient description to adequately describe the metes and bounds of any DNA "fragment" that could possibly be "derived" from undefined "regions" of the papillomavirus.

Claims 11-14, 16, 18, 19, 26 and 28-30 refer to polypeptides or proteins "derived" from

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the E6, E7, L1, IL-2, B7.1, recombinant vectors, or viruses. What does "derived" mean? Is the claim referring to a percentage of homology structural components or a similar functional characteristic to the native proteins, vectors, or viruses?

Claims 12 and 27 are indefinite because it recites an improper Markush group. The applicant is referred to MPEP 2173.05(h) and advised to reformat the claim to read "wherein R is a material selected from the group consisting of A, B, C and D" or "wherein R is A, B, C or D".

Claim 17 refers to excision "zones" of the vaccinia virus. What are these "zones"? Are they introns or non-essential portions of DNA in the vector?

Claim 20 refers to a recombinant vector that is alive or killed. The virus that the vector is derived from could be killed or attenuated. Vectors are inanimate tools used for cloning.

Claim 25 refers to nononcogenic "variants" of E6 and/or E7 proteins of a human papilloma virus. What is this "variant" referring to? Is the "variant" a protein, an isolated amino acid, or part of a nucleic acid from E6/E7? A clear definition of what is meant by a "variant" is not provided in the specification in the terms of homologous structural components or similar functionality of other substances that could define a "variant" of E6/E7.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-19, 25, 26, 28, 29, and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims 10-19, 25, 26, 28, 29, and 30 are drawn to a genus of DNA "fragments" of proteins or polypeptides "derived" from the E6, E7, L1, IL-2, B7.1, viruses, and "variants" of E6 and E7 of a human papilloma virus. The specification does not teach what structural elements of these derivations or variants or DNA "fragments" of the vaccinia virus. Since the genus embraces a wide variety of possible derivatives, variants, or fragments of each polypeptide or protein, the single species of each polypeptide, protein, or virus is not seen as representative for the full genus claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10-13, 18, 23-27, 30, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Stanley et al. in WO 96/29091.

The claims are drawn to a pharmaceutical composition intended for the prevention or treatment of a papillomavirus (HPV) infection comprising a polypeptide from E6 and/or E7 and L1 and/or L2 and a polypeptide having immunostimulatory activity, such as interleukin-12 (IL-12). All of the polypeptides are expressed recombinantly from independent expression control elements on a vaccinia vector or multiple vaccinia vectors.

Stanley et al. teaches a papilloma vaccine for the treatment of human papillomavirus infection, see page 4, lines 6-7 and 17-22. The composition comprises at least a substantial part of one of the proteins E1, E2, E4, E6, E7, L1 and/or L2 of HPV types 6, 11, 16, and/or 18, and IL-12, see page 4, lines 29-37, and claims 5, 6, 13, 15. The polypeptides are expressed by independent expression control elements with the use of a recombinant vaccinia virus vector encoding a polypeptide, antigenic fragment, or fusion protein, see page 5, lines 2-8 and claims 7, 8, 13, 16, and 17. Claim 3 further anticipates the use of IL-12 as an immunotherapeutic or as an immunostimulatory vaccine adjuvant. The patent claims clearly state that the expression vector encode at least one papillomavirus protein, clearly encompassing multiple expression vectors, each expressing a different papillomavirus protein that are not fused to each other, see page 6, line 7 and page 11, lines 21-25. In addition, Stanley et al. teaches that the composition is injected, see page 6, lines 28-31 and page 7, lines 7-15. All of the teachings of Stanley et al. anticipate claims 10-13, 18, 23-27, 30, and 31.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 10-16, 18, 19, 20, and 23-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley et al. in view of Boursnell et al. in WO 92/16636, Galloway, Hines, et al., and Gajewski.

The claims are drawn to an attenuated, recombinant Wyeth strain vaccinia vector in which the DNA fragments from the papillomavirus proteins are inserted into the thymidine kinase (TK) and/or the 7.5K promoters, thereby expressing the proteins from independent expression control elements. In addition, the claims are drawn to a pharmaceutical composition intended for the prevention or treatment of a papillomavirus (HPV) infection comprising a polypeptide from E6 and/or E7 and L1 and/or L2 and a polypeptide having immunostimulatory activity, such as interleukin-2 (IL-2), and a co-adhesion molecule B7.1.

See the teachings of Stanley et al. above. Stanley et al. teaches the use of a vaccinia virus vector in a papilloma vaccine, but does not teach which strain additionally comprising IL-2 or B7.1.

Boursnell et al. teaches a recombinant vector that expresses wild-type or mutant portions of E6 and E7 from HPV16 and HPV18 for conditions caused by an HPV infection (see page 18, lines 1-4) that have open reading frames that can be inverted with respect to one another, see page 9, lines 21-28, page 11, lines 17-23, page 12, lines 2-8, figures 15, 16, 17, 24, 26, and claims 1, 9, 11, 12, 21, and 23. Boursnell et al. teaches that the Wyeth strain of the vaccinia virus had the lowest number of complications, see page 14, lines 17-25. The insertion of foreign DNA is favored at the thymidine kinase gene locus, see page 14, lines 26-28 and page 28, lines 22-26. Boursnell et al. also teaches that the p7.5 and/or the H6 promoters may be used, see page 16, lines 11-22. Boursnell et al. does not teach the use of the capsid proteins, L1 or L2, nor does the reference teach a composition additionally comprising IL-2 and B7.1.

Galloway teaches a prospect for prophylactic vaccine to treat papillomavirus infections with a composition that includes L1 and L2 proteins and therapeutic vaccines that include E6 and

E7 proteins from the papillomavirus, see the abstract on page 187. Galloway also teaches that most individuals have antibodies that recognize the capsid proteins, especially L2, see the first paragraph of column 2 on page 189. In addition, rabbits immunized with L1 or L2 conferred protective immunity against the virus, see first full paragraph of column 2 on page 190. Galloway also teaches that L2 and E7 fusion proteins have reduced the number, severity, and duration of lesions. E7 was found to protect mice from a syngeneic tumor in an MHC-restricted fashion, see the paragraph bridging pages 190-191. Stimulation of the immune response against E6 and/or E7 may be beneficial in clearing tumors, see the next to the last sentence of the second column on page 191. From the teachings of Galloway, one of skill in the art at the time of the invention would have been motivated to combine E6, E7, L1, and/or L2 into a vaccine to treat or prevent a papillomavirus infection. One of skill in the art at the time of the invention would have had a reasonable expectation of success because of the prophylactic properties of L1 and L2 to confer immunity and the treatment of tumors demonstrated by E6 and E7. Galloway does not teach the use of IL-2 and B7.1 to aid in activating the immune response.

Hines et al. teaches that the E7 oncoprotein peptide injected into mice induces a protective cell-mediated response against tumor formation after a challenge with HPV 16-transformed tumor cells in vivo. Immunization with peptides prevents tumor formation. Hines et al also proposes cell adoptive therapy treatment to accelerate tumor regression. This is accomplished by removing a patient's serum and stimulating their lymphocytes in vitro with a peptide, E6 and E7, and a cytokine, IL-2, and returned to the cancer patient as therapy, see the "cellular adoptive therapy" section on page 862-863 and figure 2 on page 863. Hines et al. concurs with Galloway in teaching that the major capsid proteins, L1, from the papillomavirus,

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see table 1 on page 861, mimicked the conformation of intact virions and were recognized by well-defined type-specific antibodies. Immunologically active virus-like particles used in a prophylactic vaccine would be successful because they are antigenic,, protective in animal models, and lack the viral DNA that would be carcinogenic in the host. Demonstrated again by the teachings of Hines et al., one of skill in the art at the time of the invention would have had a reasonable expectation of success because of the prophylactic properties of L1 and L2 to confer immunity and the treatment of tumors demonstrated by E6 and E7. Hines et al. does not teach the incorporation of B7.1 to aid in stimulating T cells.

Gajewski teaches that T cells require the participation of one additional “second signal” to secrete IL-2. This “second signal” capable of activating CD4+ and CD8+ T cells to secrete IL-2 is B7.1 and is used as a cofactor for IL-2 production and has been found to be necessary for the production of IL-2. B7.2 is also can also provide costimulator function for IL-2 production of CD4+ cells. Gajewski goes on to teach that the this aspect of cytotoxic T lymphocytes (CTL) would have a practical application in the development of tumor-specific immunotherapy, see the introduction on page 465. Expression of B7.1 human tumor cells can render them better able to stimulate alloreactive CD8+ lymphocytes to produce their own IL-2, see the first paragraph of the discussion section on page 470. Gajewski does not teach a papillomavirus vaccine that comprises the papillomavirus proteins E6, E7, L1 and/or L2.

One of skill in the art at the time the invention was made would have been motivated to combine the teachings of Stanley et al., Boursnell, et al., Galloway, Hines et al. and Gajewski to provide a prophylactic and a treatment vaccine that would represent the major antigens of the papillomavirus and with an enhanced ability to stimulate T cells with IL-2 and B7.1 in a

recombinant vaccinia virus vector. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because of the success taught by Stanley et al., Galloway, and Hines et al. in preventing papillomavirus infections with a composition that includes L1and L2 and therapeutic vaccines that include E6 and E7 proteins from the papillomavirus. The addition of IL-2 to a vaccine composition taught by Hines et al. would be advantageous in stimulating T cell response. The importance of stimulating IL-2 was taught by Gajewski as well as the capability of B7.1 to stimulate a T cell response to produce IL-2. All of the proteins are expressed on independent control elements taught by Boursnell, et al. to decrease the likelihood of recombination. Therefore, it would be *prima facie* obvious to one skilled in the art to combine the teachings of the references to make a successful vaccine for the treatment and prevention of papillomavirus infections.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley et al., Boursnell et al., Galloway, Hines, et al., and Gajewski as applied to claims 10-16, 18-20, 23-31 above, and further in view of Meyer et al.

The claim is drawn to an MVA strain of the vaccinia virus that the papillomavirus polypeptides are inserted at the I-VI excision “zones” of the vaccinia virus.

Meyer et al. teaches six major deletion sites in the wild-type vaccinia Ankara strain during attenuation to MVA that are not essential to viral replication and attenuate virus pathogenicity, see the abstract, the results section on page 1032-1034, and the sentence bridging the columns on page 1036. Meyer et al. teaches that the insertion of the K1L gene leads to increased host range and suggests this as a selection system for recombinant viruses expressing

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foreign genes, see page 1037, a third of the way down page 1037. One of skill in the art at the time the invention was made would have been motivated to utilize the MVA strain of the vaccinia virus in a vaccine to treat the papillomavirus because of the large insertion areas provided by the non-essential viral genome that can be deleted without harming viral replication, see previous citations. Therefore, as evidenced by the references, the invention as a whole would have been *prima facie* obvious to one of skill in the art at the time of the invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 7:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
October 4, 2000

